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Pharmacokinetics of (1*R*,2*R*-diaminocyclohexane)oxalatoplatinum(II) in comparison with cisplatin following a single intravenous injection in rabbits

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Summary. The pharmacokinetics of (1*R*,2*R*-diaminocyclohexane)oxalatoplatinum(II) (1-OHP, NSC-266046), a second-generation antitumor platinum complex, was studied in rabbits and compared with that of cisplatin. The rabbits were given a single i.v. dose of 1-OHP or cisplatin (10 μmol/kg). A comparison of tissue platinum levels at 24 h postinjection showed that platinum levels were lower in the eight organs examined, which included the kidney and liver, after the injection of 1-OHP than following cisplatin administration. Plasma-decay profiles of three platinum species, that is, the unchanged species, filterable platinum, and total platinum, were examined. Plasma levels of the unchanged species and filterable platinum for 1-OHP declined more rapidly than those for cisplatin. The ratio of plasma filterable-to-total platinum indicated that the protein-binding ability of 1-OHP was greater than that of cisplatin. As for urinary excretion, amounts of the unchanged species and total platinum excreted during the 24 h period postinjection were 28% and 76% of the dose for 1-OHP and 23% and 57% of the dose for cisplatin, respectively. The renal clearance of both the unchanged species and filterable platinum in plasma for 1-OHP was about 2-fold that for cisplatin. 1-OHP is reported to be much less nephrotoxic than cisplatin. This may be due in part to its pharmacokinetic behavior or to pharmacokinetic differences resulting from chemical reactions that make 1-OHP less toxic than cisplatin.

Introduction

cis-Diamminedichloroplatinum(II) (cisplatin, CDDP) is a well-established cancer chemotherapy agent with broad use in the treatment of human malignancies [20]. However, its clinical usefulness has been limited by undesirable side effects of severe renal toxicity, nausea and vomiting, and neurotoxicity [26]. Therefore, much effort has been made to develop second-generation antitumor platinum complexes with greater antitumor activity and/or less toxicity than CDDP. (1*R*,2*R*-Diaminocyclohexane)oxalatoplatinum(II) (oxaliplatin, NSC-266046; 1-OHP), synthesized by Kidani et al. [11], is a member of this group of complexes. The structural formulae of 1-OHP and CDDP are depicted in Fig. 1. 1-OHP has completed preclinical [12, 21, 29] and phase I studies [6, 22] and is currently undergoing phase II study [23, 24]. In these studies, 1-OHP has been found to be effective against several animal and human tumor types, including human melanoma and ovarian cancer. As for the toxic side effects, no nephrotoxicity has been observed, myelosuppression has been insignificant, and nausea and vomiting have been comparable with those induced by CDDP. Another important feature is that although the development of resistance to CDDP has limited its clinical use, CDDP-resistant cell lines are sensitive to 1-OHP [29].

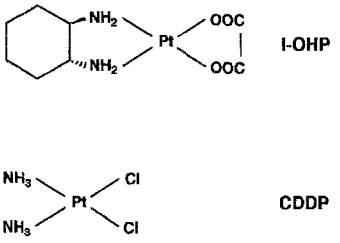

Fig. 1. Structural formulae of 1-OHP and CDDP

Clarification of pharmacokinetics is essential in the establishment of a new agent as a cancer chemotherapy drug. Platinum tissue distribution following single i. v. dosing of 1-OHP in mice has been reported [1]. However, only little is known about its plasma and urinary pharmacokinetics [23]. On the other hand, only free circulating platinum, in other words, plasma filterable platinum, has been generally considered to have cytotoxicity [2, 8]; this includes the biodegradation products yielded in the biological milieu as well as the unchanged complex. The unchanged complex

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and its biodegradation products exhibit different biological activities and different pharmacokinetic features [3, 4]. However, among the platinum species that may be present in the body, the unchanged complex is by far the most important one in antitumor activity. We have developed high-performance liquid chromatographic (HPLC) methods for determining intact 1-OHP [14] and CDDP [15] in plasma and urine. In the present study, we examined the tissue distribution, urinary excretion, and plasma decay of the unchanged species, filterable platinum, and total platinum following a single i.v. injection of 1-OHP and compared the results with those obtained for CDDP so as to reveal the pharmacokinetic features of 1-OHP in an attempt to provide an explanation for its low nephrotoxicity.

Materials and methods

Chemicals. 1-OHP was synthesized according to the reported method [11]. CDDP was purchased from Aldrich (Milwaukee, Wis., USA) and was used as received. All other chemicals were of reagent grade or better and were used as received.

Experimental protocols. Male Japanese white rabbits weighing about 2.5 kg were used in this study. 1-OHP and CDDP were dissolved at a concentration of 20 μmol/ml in 5% dextrose and 0.9% NaCl solutions, respectively. Either 1-OHP or CDDP was given to a rabbit at a dose of 10 μmol/kg weight via the left ear vein, immediately followed by the injection of 0.5 ml/kg 0.9% NaCl solution (1-OHP-treated rabbits) or 5% dextrose solution (CDDP-treated rabbits) via the left ear vein.

Blood (about 2 ml) was collected at intervals from the right ear vein into an ice-cooled heparinized tube and was immediately centrifuged at 2000 *g* for 3 min at 4° C to obtain plasma. A portion of the plasma was then immediately analyzed for total platinum concentration. Another portion of the plasma was immediately centrifuged at 3000 *g* for 15 min at 4° C in an Amicon micropartition-system starter kit (MPS-1) fitted with a YMT membrane (Danvers, Mass., USA) to obtain ultrafiltrate. The plasma ultrafiltrate was immediately analyzed for concentrations of the unchanged complex and filterable platinum. Urine was collected into an ice-cooled tube as 20-min specimens via a cannula placed in the bladder through the urethra during the first 5 h after the injection. Subsequent urine samples were collected from the metabolic cage. The urine samples were immediately analyzed for concentrations of the unchanged complex and total platinum. Rabbits under ether anesthesia were killed on days 1, 3, or 5. Tissue samples were immediately removed and stored at –20° C until total platinum concentration was measured.

Sample analysis. Concentrations of intact 1-OHP and CDDP in plasma and urine were determined by the HPLC methods described in our previous papers [14, 15]. The following methods were used to determine 1-OHP levels in plasma and urine. In brief, 1-ml aliquots of the plasma and urine samples obtained were immediately loaded onto pretreatment columns composed of Dowex 1-x8 (an anion-exchange resin), Dowex 50W-x4 (a cation-exchange resin), and a SEP-PAK C_{18} cartridge, and 1-OHP was then eluted with water. The 1-OHP-containing fraction of the effluent was collected and subjected to HPLC immediately. This pretreatment procedure was carried out at 4° ± 2° C. The HPLC conditions were as follows: the analytical column was a Finepak SIL C18 (4.6 mm inside diameter × 25 cm; Jasco, Tokyo, Japan) column maintained at 40° C, the eluent was water/methanol (95 : 5 v/v) delivered at a flow rate of 1 ml/min, the sample injection volume was 100 μl, and the detection wavelength was 210 nm. Under these conditions, linear calibration curves for 1-OHP in plasma and urine were obtained at a concentration range of 0.5 – 100 μM, and the recovery values obtained in an addition/recovery study were more than 80%, with the coefficient of variation being less than 4%, as previously described [14].

Total platinum concentration was determined using an atomic absorption spectrophotometric method [13]. Briefly, 1-ml aliquots of plasma and urine samples or 1 g of tissue samples were placed in 30-ml Kjeldahl flasks, and 100 μl 1.703-mM nickel nitrate solution (10 μg nickel) was then added to the flasks as the internal standard. Samples were digested with nitric acid and hydrogen peroxide. Acid digests were evaporated to dryness, and the residues were dissolved in 1 ml 1 *N* nitric acid. Analyses of platinum and nickel were made on a Hitachi model Z-8000 atomic absorption spectrophotometer with Zeeman background correction (Hitachi, Japan). The platinum concentration in a sample was obtained by correcting the measured platinum level by the measured nickel level. Plasma ultrafiltrate samples were directly analyzed for platinum concentration without prior acid digestion or internal standard correction.

Data analysis. Pharmacokinetic parameters were calculated using the nonlinear least-squares fitting program MULTI [31]. The plasma concentrations found for the unchanged species and filterable platinum in individual rabbits were fitted to the equation $C = Ae^{-\alpha t}+Be^{-\beta t}$ or $C = Ae^{-\alpha t}$, where C (nanomoles per milliliter) is the concentration at time t (minutes) and A, B (nanomoles per milliliter) and α, β (minutes^{-1}) are the concentration and rate constants, respectively. The area under the concentration-time curve (AUC_t, nanomoles times minutes per milliliter) was calculated using the formula $AUC_t = \int_0^t C dt$, where C (nanomoles per milliliter) is the concentration at time t (minutes). Renal clearance (CLr_t, milliliters per minute per kilogram) was calculated using the equation $CLr_t = Xu_t/AUC_t$, where Xu_t (nanomoles per kilogram) is the amount of platinum species excreted in urine up to time t after the injection. Whole-body clearance (CLw, milliliters per minute per kilogram) was calculated using the equation $CLw = dose/AUC_\infty$. ΔCL (milliliters per minute per kilogram) is the difference between whole-body clearance and renal clearance. Student's t-test was used for the statistical analysis, whereby a value of $P < 0.05$ was considered to be significant.

Results

Platinum concentrations measured in eight tissues on days 1, 3, and 5 are listed in Table 1. 1-OHP and CDDP showed a similar order of decreasing tissue platinum levels in that the platinum concentration was highest in the kidney followed by the liver, whereas other organs had approximately the same levels. On the other hand, platinum levels in the kidney and liver on days 1, 3, and 5 were significantly lower after the injection of 1-OHP than following CDDP administration, with the former amounting to roughly half of the latter. As for other organs, although 1-OHP produced lower platinum levels than did CDDP in the small intestine, bladder, and testicle on day 1, the difference was not significant either in those organs on days 3 or 5 or in the lung, stomach, and spleen on days 1, 3, or 5. Platinum levels in brain and muscle, not shown in the table, were below the detection limit (0.1 ppm) for both compounds. In contrast to the present study, in a previous study using mice, the highest platinum level was observed in the spleen followed by the kidney [1]. There may be a species difference in platinum tissue distribution following i.v. dosing of 1-OHP. This discrepancy may be also due in part to the difference in handling of tissue samples: dried samples were used for platinum analysis in the previous study as opposed to wet ones in this study.

Profiles of the cumulative urinary excretion of two forms of platinum, namely, the unchanged species and total platinum, are given in Fig. 2. The amounts of unchanged species and total platinum excreted during the first 1 h after

Table 1. Tissue distribution of platinum on days 1, 3, and 5 in rabbits given a single i. v. dose of 10 μmol/kg 1-OHP or CDDP

Tissue	Day	Platinum concentration (ppm)	
		1-OHP	CDDP
Kidney	1	5.3 ± 0.5**	10.3 ± 1.8
	3	2.7 ± 1.0*	5.5 ± 0.9
	5	1.7 ± 0.6*	2.8 ± 0.1
Liver	1	1.1 ± 0.1**	3.4 ± 0.8
	3	0.8 ± 0.2**	2.8 ± 0.5
	5	0.6 ± 0.2**	2.1 ± 0.4
Testicle	1	0.5 ± 0.1**	1.1 ± 0.3
	3	0.4 ± 0.1	0.6 ± 0.1
	5	0.3 ± 0.1	0.5 ± 0.1
Small intestine	1	0.7 ± 0.3*	1.5 ± 0.3
	3	0.6 ± 0.1	0.5 ± 0.1
	5	0.4 ± 0.1	0.3 ± 0.1
Bladder	1	0.8 ± 0.2*	1.5 ± 0.5
	3	1.0 ± 0.3	0.8 ± 0.1
	5	0.6 ± 0.1	0.7 ± 0.1
Lung	1	0.9 ± 0.3	1.2 ± 0.2
	3	0.4 ± 0.1	0.5 ± 0.2
	5	0.4 ± 0.1	0.4 ± 0.2
Stomach	1	1.0 ± 0.5	1.3 ± 0.2
	3	0.8 ± 0.1	0.6 ± 0.1
	5	0.5 ± 0.1	0.4 ± 0.1
Spleen	1	1.5 ± 0.3	1.4 ± 0.6
	3	1.2 ± 0.3	1.0 ± 0.2
	5	0.9 ± 0.2	0.9 ± 0.4

Data represent mean values ± SD obtained for three rabbits
* Significantly different from the values for CDDP (P <0.05),
** significantly different from the values for CDDP (P <0.01)

injection were 27.7% ± 2.7% and 55.4% ± 4.4% of the dose for 1-OHP and 18.1% ± 2.7% and 33.2% ± 4.4% of the dose for CDDP, respectively. For 1-OHP, urinary excretion was significantly more rapid initially than that for CDDP, especially during the 1st h postinjection, but was comparable with that for CDDP thereafter. The amounts of total platinum excreted during the 24-h period postinjection were 76.2% ± 4.7% and 57.5% ± 6.6% of the dose for 1-OHP and CDDP, respectively. Although more than 60% of the urinary platinum was present as the unchanged species during the first 0–20 min after the injection of 1-OHP and CDDP, the former showed a more rapid decrease in the proportion of the unchanged species to total platinum than did the latter. The unchanged species was detectabel for up to 100 min after the injection of 1-OHP and for up to 240 min following CDDP administration. The amounts of unchanged species excreted in urine were 28.1% ± 2.7% for 1-OHP and 22.6% ± 2.7% for CDDP.

Plasma-decay profiles of three platinum species, namely the unchanged species, filterable platinum, and total paltinum, are shown in Fig. 3. The total platinum levels decreased in a biexponential fashion for both 1-OHP and CDDP. The unchanged species and filterable platinum were detectable for up to 60 min postinjection for 1-OHP and for up to 90 min postinjection for CDDP. The decay of these two species was biexponential in the case of 1-OHP and monoexponential in the case of CDDP, as has pre-

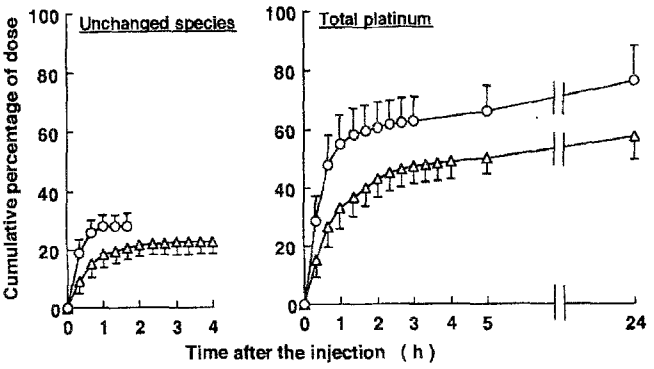

Fig. 2. Urinary excretion of the unchanged species (*left*) and total platinum (*right*) in rabbits given a single i. v. dose of 10 μmol/kg 1-OHP or CDDP. Each point represents the mean value ± SD obtained for four rabbits. ○, 1-OHP; △, CDDP

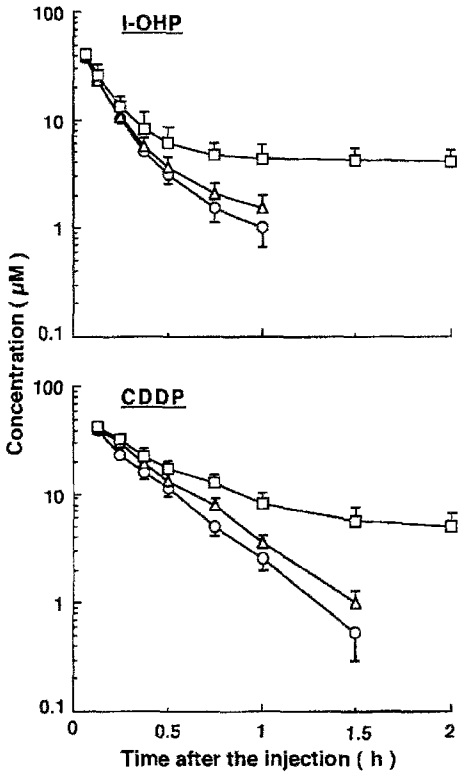

Fig. 3. Time courses of plasma concentrations of the unchanged species, filterable platinum, and total platinum in rabbits given a single i. v. dose of 10 μmol/kg 1-OHP (*top*) or CDDP (*bottom*). Each point represents the mean value ± SD obtained for four rabbits. ○, Unchanged species; △, filterable platinum; □, total platinum

viously been reported [22, 25, 28]. The parmacokinetic parameters (A, α, B, β) and AUC_{90} values (defined in Materials and methods) for these species are listed in Table 2. The disappearance of the unchanged species and filterable platinum was significantly more rapid after 1-OHP injection than following CDDP administration and, consequently, the AUCs of these species were significantly smaller for 1-OHP than for CDDP. On the other hand, the ratios of plasma filterable-to-total platinum at 15, 30, 45, and 60 min postinjection were 0.70 ± 0.07, 0.60 ± 0.05, 0.44 ± 0.05, and 0.35 ± 0.05 for 1-OHP and

Table 2. Pharmacokinetic parameters of the unchanged species and filterable platinum in plasma for 1-OHP and CDDP

	A (nmol/ml)	α (min^{-1})	B (nmol/ml)	β (min^{-1})	AUC_{90} (nmol min ml^{-1})	CLr_{60} (ml min^{-1} kg^{-1})	CLw (ml min^{-1} kg^{-1})	ΔCL (ml min^{-1} kg^{-1})
Unchanged species:								
1-OHP	59.7±2.5	0.158±0.014	7.1±2.3	0.033±0.007	589± 60**	5.7±0.6**	16.9±1.7**	11.1±1.2**
CDDP	55.8±2.4	0.053±0.004			1046±138	2.6±0.3	9.5±1.0	7.0±0.8
Filterable platinum:								
1-OHP	60.0±2.6	0.155±0.013	6.5±1.9	0.025±0.006	621± 68**	12.9±1.4**		
CDDP	58.1±2.2	0.046±0.004			1243±141	5.4±0.6		

Data represent mean values ± SD obtained for three rabbits
** Significantly different from the values for CDDP ($P < 0.01$)

0.91 ± 0.05, 0.77 ± 0.03, 0.62 ± 0.03, and 0.44 ± 0.02 for CDDP, respectively. This indicates that the protein-binding ability of 1-OHP is greater than that of CDDP.

The renal and whole-body clearance values determined for plasma platinum species are listed in Table 2. The renal clearance of the unchanged species and filterable platinum was calculated as CLr_{60} since there were noticeable differences in the kinetic behavior of 1-OHP and CDDP for up to 60 min postinjection, as can be seen in Figs. 2 and 3. Whole-body clearance was calculated only for the unchanged species since it involves a pathway to convert one species to another. 1-OHP gave significantly greater CLr_{60} and CLw values than did CDDP.

Discussion

We used a 0.5% dextrose solution as the vehicle for administration of 1-OHP, as 1-OHP yielded a yellow precipitation during dissolution when physiological saline was used as the vehicle. The elemental analysis revealed that the precipitation was (1*R*,2*R*-diaminocyclohexane)-dichloroplatinum(II), and it has been reported that 1-OHP suffers substitution of the oxalato ligand by chloride ions in saline [10]. However, CDDP was dissolved in 0.9% saline as is the norm. The effect of the NaCl concentration in a vehicle on the renal toxicity and the pharmacokinetics of CDDP has been evaluated [5, 17, 25]. Therefore, we injected additional 0.9% saline into 1-OHP-treated rabbits and 5% dextrose solution into CDDP-treated rabbits immediately after the injection of either platinum complex so as to cancel the difference in vehicles.

This study was carried out using rabbits, as accurate calculation of the renal clearance of the unchanged species requires that urine samples be collected at the shortest intervals possible. The results obtained for CDDP are in general accordance with those previously reported [8, 9, 18, 19]. The present study revealed that the pharmacokinetic behavior of 1-OHP was significantly different from that of CDDP.

The kidney was the major platinum-excretion route for both 1-OHP and CDDP, with more than 50% of the dose being excreted during the first 5 h after injection. One characteristic of 1-OHP pharmacokinetics is that the renal clearance of both the unchanged species and filterable platinum in plasma is greater than that observed after CDDP administration. Diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin, CBDCA), a second-generation antitumor platinum complex, is a dicarboxylato complex that is much less nephrotoxic than CDDP [7]. Although pharmacokinetic data for CBDCA are not available from the present study, some studies on the urinary excretion of CBDCA indicate that its renal clearance is greater than that of CDDP [18, 27, 28]. These studies also suggest that renal toxicity is not solely a function of the platinum concentration in the kidney but rather is related to the urinary excretion mechanism or intrinsic nature of the complex given.

The platinum tissue distribution of 1-OHP was also characteristic as compared with that of CDDP. As listed in Table 2, the ΔCL value obtained for the unchanged species by subtracting CLr_{60} from CLw was greater for 1-OHP than for CDDP. Although biotransformation as well as tissue distribution are important pathways involved in ΔCL, the ratios of plasma unchanged-to-filterable platinum indicated that there was no significant difference in the biotransformation rate of the unchanged species following 1-OHP versus CDDP administration. The ratios determined at 15, 30, 45, and 60 min postinjection were 0.96 ± 0.06, 0.86 ± 0.06, 0.75 ± 0.08, and 0.67 ± 0.08 for 1-OHP and 0.78 ± 0.05, 0.83 ± 0.06, 0.66 ± 0.06, and 0.70 ± 0.09 for CDDP, respectively. These data on ΔCL and the ratios indicate that distribution of the unchanged species to tissues is more rapid for 1-OHP than for CDDP. 1-OHP nevertheless yielded lower platinum levels in the kidney and some other organs on day 1, as can be seen from Table 1, suggesting that the effusion of platinum into those organs occurred more rapidly after the injection of 1-OHP. The features of platinum tissue distribution observed for 1-OHP are considered to play a part in its low nephrotoxicity and to be associated with its greater renal clearance, although the plasma data indicate that 1-OHP has a higher protein-binding capacity than does CDDP and this may seem to be inconsistent with the above features. 1-OHP has a 1*R*,2*R*-diaminocyclohexane carrier ligand, which is more hydrophobic than those of CDDP. Although the mechanism by which 1-OHP differs from CDDP in its platinum tissue distribution remains unknown, the hydrophobicity of the carrier ligands of 1-OHP and CDDP may be involved.

Other features of 1-OHP pharmacokinetics were observed in the plasma decay of the three platinum species examined in this study. 1-OHP showed a faster decline of plasma concentrations of the unchanged species and filter-

able platinum. This reflects that the renal and whole-body clearance of those platinum species is greater for 1-OHP than for CDDP, as described above. On the other hand, the ratios of plasma filterable-to-total platinum were smaller for 1-OHP than for CDDP, indicating that the binding of platinum to rabbits' plasma proteins occurs more rapidly after 1-OHP injection than following CDDP administration. Although CBDCA has a dicarboxylato-*O,O'* coordination structure similar to that of 1-OHP, it has been reported to yield much slower binding of platinum to plasma proteins than does CDDP in vivo [27] or in vitro [30]. It has been suggested that the degree of protein binding of platinum complexes is related to the lability of their leaving groups [30]. The stability of 1-OHP and CBDCA in physiological saline may be a reflection of their plasma protein-binding ability. In physiological saline, 1-OHP disappears with a half-life of about 11 h at 25°C [10], whereas CBDCA is stable for 7 days at 37°C [16].

The present study revealed further aspects of the pharmacokinetics of 1-OHP by comparing the latter with that of CDDP. It was found that the renal clearance, whole-body clearance, and plasma protein binding of the unchanged species and filterable platinum in plasma were greater after the injection of 1-OHP than following CDDP administration. The platinum tissue distribution of 1-OHP was different from that of CDDP. Moreover, these features indicate that the low nephrotoxicity of 1-OHP as compared with CDDP is due in part to its pharmacokinetic behavior or that pharmacokinetic differences result from chemical reactions that make 1-OHP less toxic than CDDP. To clarify the pharmacokinetics of 1-OHP in detail, further studies must be conducted that include other platinum complexes such as CDDP, CBDCA, and tetrachloro(1*R*,2*R*-diaminocyclohexane)platinum(IV) (tetraplatin). 1-OHP is currently undergoing phase II study. Studies of its clinical pharmacokinetics should also be undertaken to establish an optimal therapeutic protocol.

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